IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Darrell R. Anderson et al.

Group Art Unit: 1644

Application No. 08/746,361

Examiner: P. Gambel

Filed: November 8, 1996

Title: IDENTIFICATION OF UNIQUE BINDING INTERACTIONS BETWEEN CERTAIN ANTIBODIES AND THE HUMAN B7.1 AND B7.2 CO-STIMULATORY ANTIGENS

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DECLARATION OF DARRELL R. ANDERSON, Ph.D.

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, declare and state as follows:

1. That I am the same Darrell R. Anderson who is an inventor of the above-identified application.

2. That I understand that the Examiner has maintained his position that it allegedly would have been obvious to have derived monoclonal antibodies that specifically inhibit the interaction of B7.1 antigens with CD28, but which do not inhibit the interaction of B7.1 antigens with CTLA-4 as of the time this application was filed. The Examiner relies especially on a patent assigned to Chiron, which names deBoer et al. as the inventors, U.S. Patent 5,757,034, and a patent assigned to Bristol Meyer Squibb, by Linsley et al., U.S. Patent 5,770,197. The Examiner states particularly in the most recent Office Action that the subject antibodies are unpatentable because Linsley et al. purportedly suggests the use of anti-B7.1 antibodies to inhibit interactions of CD28-positive cells "or" CTLA-4-positive cells with B7 cells and that this provides a "reasonable expectation of success" (the generation of antibodies that selectively inhibit interaction of B7.1 with CD28 but which do not inhibit interaction of B7.1 with CTLA-4.) I respectfully disagree.

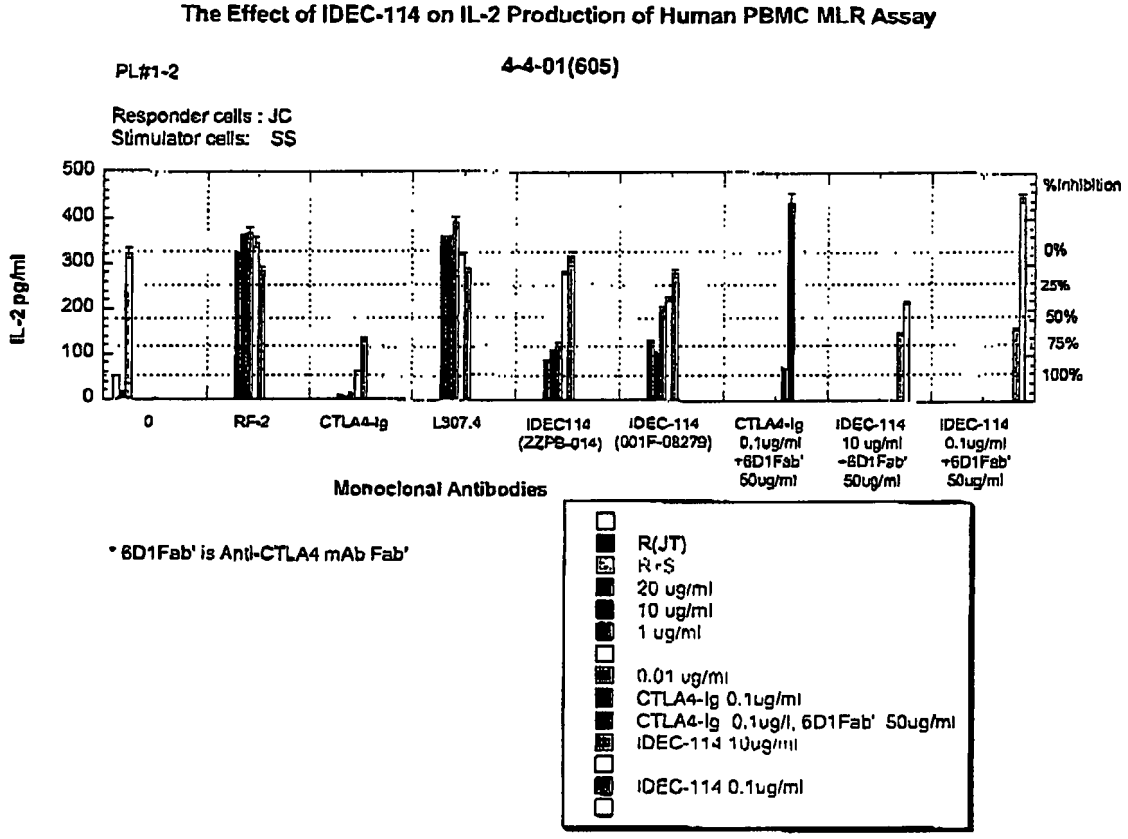
3. I have carefully reviewed the Linsley et al. and DeBoer patents, including the passages at Col. 15, para. 7 (lines 60-65) relied upon by the Examiner. In my estimation as an expert in the field of co-stimulatory molecules, recombinant antibodies and their potential use as therapeutic, at best these references teach that B7.1 was known to interact with CTLA-4 and CD28 and that anti-B7.1 antibodies potentially could be obtained which inhibit such interactions. However, these references fail to provide a reasonable expectation that antibodies could be obtained that *selectively* inhibit the interaction of B7.1 with CD28, but which do not inhibit the interaction of B7.1 with CTLA-4. Particularly, there is no teaching that a separate and distinct epitope on human B7.1 exists which is instrumental in CD28 interaction, to which an antibody could be generated against and that such antibody will not inhibit the interaction of B7.1 with CTLA-4.

4. In my opinion, the non-trivial and unexpected nature of the outcome is strongly supported by the fact that even to date, the antibodies disclosed by us in this application are the only known anti-B7.1 antibodies reported that exhibit this unique and desirable binding characteristic.

5. It is further my opinion, that the unexpected nature of the outcome is supported by the manner that subject antibodies were obtained. Particularly, the subject antibodies were generated in cynomolgus monkeys. With respect thereto, it should be emphasized that cynomolgus monkey and human antigens are typically highly evolutionarily conserved. For example, the variable regions of antibody sequences between these species exhibit on average $\leq$ from between 85-98% sequence identity. Thus, B7.1 antigens in humans and cynomologus monkeys would similarly be expected to be highly conserved. Given this expectation, it would have been predicted that the human B7.1 antigen will present very few epitopes that would be recognized as foreign in a cynomolgus monkey. This renders

the outcome even more unexpected, i.e., that a cynomolgus monkey would produce antibodies against an epitope that was never even known to exist even when B7.1 was utilized as an immunogen in species much more evolutionarily removed from humans (rodents). Particularly, as established by my earlier declaration, all prior art of which I am aware relating to B7.1 antibodies (which have been produced in rodents) cross-react with CTLA-4. This makes the inventive result even more unexpected.

6. I further believe that the subject antibodies constitute a significant advance in the field because they exhibit distinct functional characteristics vis-à-vis anti-B7.1 antibodies that interact with CTLA-4. This difference is substantiated by the functional behavior of an antibody according to the invention (referred to as 16C10 in the application and more recently referred to by the subject Assignee as IDEC-114) to another anti-B7.1 antibody reported by Nickoloff et al. that blocks B7.1 interaction with CTLA-4. These anti-B7.1 antibodies as well as a positive control (CTLA-4-Ig fusion protein) and a negative control (irrelevant human IgG antibody to RSV fusion protein, RF2) were compared in a number of mixed lymphocyte reactions (MLRs). The results of a representative MLR experiment comparing these immune molecules are set forth on the following page:



It can be seen therefrom that CTLA-4Ig, blocked both B7-1 and B7-2 interactions with CD28 (positive control). It can also be seen that while IDEC-114 effectively blocked IL-2 production when B7.2 antigens were present, the other anti-B7.1 antibody (L307.4) had no such inhibitory effect. Similar results were obtained with other MLRs run by us under the same conditions. These results clearly show that antibodies according to the invention exhibit differences functional properties and mechanisms relative to previous other anti-B7.1 antibodies. In my opinion, these differences are unexpected and are most probably a consequence of the unique binding interaction of the subject anti-B7.1 antibodies.

7. It further has recently been shown that anti-B7.1 antibodies according to the invention exhibit in vivo characteristics that support their clinical use for treatment of T cell mediated disorders such as psoriasis. Evidence relating thereto is contained in a draft

manuscript attached to this Declaration as Exhibit A. This manuscript contains preliminary clinical trials wherein IDEC-114 was administered to 24 psoriasis patients (open-label, single dose, dose-escalatory study in patients with moderate to severe chronic plaque psoriasis.) Based on the observed "Psoriasis Area and Severity Index", "Physician's Global Assessment", and "Psoriasis Severity Scale", which comprise an accepted means for evaluating the prognosis of psoriasis patients, IDEC-114 appears to be safe, well-tolerated and exhibits promising clinical activity (average plaque thickness and plaque CD3+/CD8+ T cell numbers decreased in patients administered 10 mg/kg of IDEC-114). (See results in Exhibit). These results support a conclusion that anti-B7.1 antibodies according to the invention will provide an effective therapy for treatment of psoriasis as well as other T cell mediated diseases.

8. I also understand that the Examiner has cited our earlier patent as prior art to the claimed invention. With respect thereto, it should be noted that the additional inventor, William Shestowsky, was a named inventor on the earlier patent because of his contribution to the particular antibody sequences that were claimed therein. However, he is properly not a named inventor with respect to the subject claims, none of which are directed to these specific antibody sequences. Thus, the disclosure in our earlier patent does not constitute work by another within the context of the present invention.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the

United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Date: 9/24/01

Darrell R. Anderson, Ph.D.